Assessment of cognitive functions in children on regular hemodialysis and after renal transplantation

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Received 6 December 2016
Accepted 17 April 2017

Middle East Current Psychiatry
2017, 24:128–133

Background
End-stage renal disease is a complicated disorder associated with specific problems occurring in children, such as impaired growth and psychosocial adjustment, in addition to cognitive affection. The lifespan and outcome of end-stage renal disease children have improved markedly since the development of dialysis techniques and kidney transplantation. The aim of our study was to compare cognitive functions in children on regular hemodialysis (HD) with children after successful renal transplantation (RTx).

Patients and methods
This study was carried out at the center of Paediatric Nephrology and Transplantation, Cairo University, where 20 children on regular HD, 20 children after successful RTx, and 20 children as healthy controls were assessed. The Wechsler Intelligence Scale for Children was used for the assessment of cognitive functions.

Results
Children on regular HD and those after successful RTx were found to have a significant impairment in cognitive functions in all subtests including the full-scale intelligent quotient, verbal intelligent quotient, and performance intelligent quotient among HD and post-RTx patients compared with the healthy controls. Also, impaired cognitive functions were significantly lower in the children on dialysis compared with the post-RTx group.

Conclusion
Children on regular HD and after successful RTx have more impaired cognitive functions than healthy controls.

Keywords:
children, cognitive functions, hemodialysis, renal transplantation

Middle East Curr Psychiatry 24:128–133
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2090-5408

Introduction

Chronic kidney disease (CKD) is defined as slow and progressive deterioration of kidney functions that is typically irreversible. The severity of CKD is defined by a decrease in the glomerular filtration rate persisting for 3 or more months [1].

Similar to children with other chronic progressive illnesses, the cross-sectional studies of children with CKD suggest that there is an increased risk for a wide range of delays in motor and cognitive development, particularly for children with end-stage renal disease (ESRD) [2,3].

Age of onset of ESRD is associated with outcome. Children with congenital ESRD had poorer fine motor coordination and more difficulty on tests of verbal and nonverbal long-term memory than children with acquired ESRD [4,5].

Neurocognitive difficulties have long been observed in the CKD population. Although the identification and treatment of specific comorbidities of CKD (e.g. anemia) have yielded improvements in the overall functioning of this population, reports of neurocognitive deficits in children with CKD continue to emerge. These neurocognitive deficits undoubtedly will have significant lifelong implications for the CKD population as they transition to adulthood [6,7].

Transplantation can improve developmental, psychosocial, and neuropsychological outcomes, although persistent neuropsychological deficits have been reported following successful renal transplantation (RTx) [8,9].

Advances in medical care, including improvements in dialysis and transplantation, have increased the survival rates for children with ESRD. This long survival increases the opportunities for the development of psychiatric morbidity among these children. However, it is clear that this chronic disease has adverse effects on growth and development, and results in an increased risk for developmental delay, neurological abnormalities, and neuropsychological deficits [9,10,11]. Thus, the aim of this study was to compare cognitive functions in children on regular hemodialysis (HD) with children after successful RTx.

 DOI: 10.1097/01.XME.0000516380.52486.97

Patients and methods

A cross-sectional comparative study was carried out at the Centre of Paediatric Nephrology and Transplantation, Children's Hospital, Faculty of Medicine, Cairo University, from March to September 2014. The study included 40 patients diagnosed with chronic renal failure. All patients were diagnosed by nephrologists according to the definition of The Kidney Disease Outcomes Quality Initiative working group of the National Kidney Foundation [12].

Inclusion criteria

(1) Age range between 6 and 16 years.
(2) Children on regular HD for more than 1 year.
(3) Children after successful RTx more than 1 year.

Exclusion criteria

(1) Patients on peritoneal dialysis.
(2) Mental retardation.
(3) Disturbed conscious level at the time of assessment.

Patients were further subdivided into two groups as follows:

Group I: The hemodialysis group included 20 patients. The children were dialyzed for 4 h three times; proper efficient dialysis was determined by a KT/V value higher than 1.2%. A large number of these patients came from another governorate (far from Cairo) and refused to undergo the psychological tests on any other day other than the day of the dialysis session; thus, the psychological tests were performed on the same day as the dialysis session. Some patients underwent the test before the session of dialysis and others underwent the test after the session. All patients were taking calcium-based phosphate binders, calcitriol, and iron, orally, erythropoietin subcutaneously, and antacids.

Group II: The post-RTx group included 20 patients. The patients were enrolled from the RTx outpatient clinic, center of Paediatric Nephrology and Transplantation, Children's Hospital, Cairo University. The patients enrolled during their regular visiting for follow-up of their condition after transplantation almost every month for regular laboratory testing and check-up.

The healthy control group included 20 patients. They were matched for age, sex, and social class. They were recruited from the general pediatric outpatient clinic.

Methods of the study

All the groups studied were subjected to the following: detailed assessment of history, with a special focus on age, sex, and cause of renal failure, history of steroid treatment (dose and total duration), age of first HD, and duration of HD in the first group and the date of RTx in the second group. The Wechsler Intelligence Scale for Children, 3rd ed. (WISC-III) by Wechsler [13] was used for the groups studied to assess cognitive functions.

Statistical analysis

Data were tabulated and subjected to a computer-assisted statistical analysis using Microsoft Excel, version 2003, and the statistical package for the social science (SPSS; SPSS Inc., Chicago, Illinois, USA) for Windows, version 16.0. Nominal data were expressed as frequency and percentage and were compared using χ^2-tests. Numerical data were expressed as mean and SD, and were compared using independent samples *t*-tests. *P*-values less than 0.05 were considered significant.

Ethical consideration

Children participated in the study after obtaining informed consent from their parents; the research was approved by the Ethical and Research Committee, Faculty of Medicine, Cairo University. It was stated that participation in the study was voluntary and that they could withdraw from the assessment at any time.

Results

Data of 40 patients were analyzed; there were 17 (28.3% of the sample) girls and 43 (71.7% of the sample) boys. The mean age of the children in the HD group was 11.44 ± 3.03 years, the mean age of the children in the post-RTx group was 11.75 ± 3.09, and the mean age of the children in the healthy control group was 9.80 ± 3.34 years, with no statistically significant difference .There were 17 males versus three females in the control group. There was no significant difference between the studied groups and the healthy controls in terms of age and sex.

In the HD group, the mean duration of HD was 61.10 ± 34.10 months whereas in the post-RTx group, the mean post-transplantation duration was 28.10 ± 10.47 months.

In terms of the etiology of chronic renal failure in the HD group, the majority of patients had unknown etiology, 13 (65%) patients, and 45% of the patients in the post-RTx group had congenital anomalies of the kidney and urinary tract. There were no statistically significant differences between both groups in terms of the etiology.

There was a statistically significant difference between the HD group, the post-RTx group, and the control group in terms of poor school performance (school attendance and academic problems), where among the children in the HD group, there was poor school performance, eight patients, representing 40% of the sample, in the post-RTx group, only two patients, representing 10% of the sample, had poor school performance, and in the control group, only one patient, representing 5% of the sample, had poor school performance.

In terms of parents' education, in the HD group, 60% of the parents were not educated, in the post-RTx group, 25% of the parents were not educated, and in the healthy control group, 5% of the parents were not educated. There was a statistically significant difference in caregiver (parents) education between the three different groups.

The Wechsler Intelligence Scale subtests (Table 1) showed a statistically significant difference for all the subtests and also in full-scale intelligent quotient (FSIQ), performance intelligent quotient (PIQ), and verbal intelligent quotient (VIQ) (Table 1).

In terms of IQ classifications according to the Wechsler Intelligence Scale among different groups, there were a statistically significant difference for the FSIQ, PIQ, and VIQ among all groups (Table 2).

In the HD group, there was a negative correlation between the duration of HD and the score of the subtests of the WISC; however, there was no statistically significant difference (Tables 3).

There was a positive statistically significant correlation between post-RTx duration and the following subtests of the WISC: comprehension, similarities, vocabulary, picture completion, and picture arrangement; also, there was a statistically significant positive correlation between post-RTx duration, VIQ, and FSIQ (Tables 3 and 4).

Discussion

Children with renal disease in all stages of therapy (predialysis, dialysis, and transplant) performed worse than controls on a series of neuropsychological tests and that some difference increased over time [14]. The aim of our study was to compare cognitive functions in children on regular HD with children after successful RTx.

There was a significantly poor school performance (school attendance and academic problems) among the patients than in the control group; in the HD group, eight patients showed poor school performance, representing 40% of the sample, in the post-RTx group, only two patients showed poor school performance, representing 10% of the sample, and in the control group, only one patient showed poor school performance, representing 5% of the sample, with a statistically significant difference between the HD group, the post-RTx group, and the control group.

Poor school performance may be attributed to patients' psychological conditions and their caregiver as mentioned in the study by Kogon *et al.* [15]. In their study, a total of 344 patients with CKD completed the Children's Depression Inventory. Eighteen (5%) patients had elevated depressive symptoms and another seven patients (2%) were being treated for depression. In adjusted analyses, maternal education beyond high school was associated with 5% lower Children's Depression Inventory scores. Depression was associated with lower IQ (99 vs. 88; $P = 0.053$), lower achievement (95 vs. 77.5; $P < 0.05$), and lower health-related quality of life by parents and children reports. Children with depression had lower psychoeducational skills and worse health-related quality of life [15].

The impairment in cognitive functioning can also be attributed to the effect of uremic toxins on neurons. Cerebrovascular disease is a major risk factor for the development of cognitive impairment [16].

Also, growth retardation in chronic renal disease has an adverse impact on morbidity and mortality rates, quality of life, and education; also, other complications may occur such as anorexia, malnutrition, inflammation, decreased residual renal function, dialysis frequency and adequacy, renal anemia, metabolic acidosis, fluid/electrolyte imbalance, renal osteodystrophy, growth hormone, and insulin-like growth factor-1 resistance. The main factors that influence growth after RTx are the age of the recipient and the dosage of glucocorticoid drugs with a negative effect [17]. A high prevalence of global cognitive and executive impairment was detected in 56 chronic HD patients; an association was found between mild chronic hyponatremia and impaired functional status [18].

There was a statistically significant difference in caregiver (parents) education between the different groups as 60% of the parents in the HD group were not educated, whereas 25% of the parents of the post-RTx group were not educated. This could explain why poor school performance was lower in children in the post-RTx group and the control group compared with the HD group

Table 1 Means of the Wechsler Intelligence Scale subtests between the hemodialysis, post-renal transplantation, and control groups

The Wechsler Intelligence Scale subtests	HD group (mean ± SD)	Post-RTx group (mean ± SD)	Healthy control group (mean ± SD)	*P*-value
Information	6.90 ± 2.77	11 ± 4.21	13.90 ± 4.52	0.000
Comprehension	6.70 ± 3.06	8.40 ± 3.62	11.52 ± 3.18	0.009
Arithmetic	4.65 ± 2.30	7.15 ± 3.39	8.70 ± 2.62	0.000
Similarities	9.15 ± 4.25	11.40 ± 2.93	13.65 ± 3.17	0.001
Vocabulary	5.55 ± 3.28	7.40 ± 3.32	9.60 ± 2.58	0.001
Digit span	6.25 ± 2.47	8.45 ± 3.56	8.50 ± 2.04	0.012
Picture completion	5.20 ± 2.44	8.60 ± 2.48	11.30 ± 2.99	0.000
Picture arrangement	2.80 ± 2.33	3.90 ± 2.25	6.70 ± 2.36	0.000
Block design	7 ± 1.59	7.75 ± 3.40	10.45 ± 2.54	0.001
Object assembly	2.55 ± 2.01	5.75 ± 3.48	5.65 ± 2.46	0.000
Coding	2.35 ± 1.87	5.85 ± 3.28	6.85 ± 2.25	0.000
Mazes	3.65 ± 1.60	5.95 ± 2.16	7.90 ± 1.68	0.000
PIQ	63.50 ± 12.79	82 ± 18.44	98.20 ± 14.85	0.000
VIQ	86.05 ± 16.20	104.15 ± 15.02	117.60 ± 16.94	0.000
FSIQ	73 ± 14.99	92.75 ± 17.49	108.80 ± 15.58	0.000

FSIQ, full-scale intelligent quotient; HD, hemodialysis; PIQ, performance intelligent quotient; RTx, renal transplantation; VIQ, verbal intelligent quotient.
Significance at $P < 0.05$.

Table 2 The Wechsler Intelligence Scale between the hemodialysis group, post-renal transplantation group, and the control group for full-scale intelligent quotient, performance intelligent quotient, and verbal intelligent quotient

IQ classifications	HD group [*n* (%)]	Post-RTx group [*n* (%)]	Healthy control group [*n* (%)]	*P*-value
FSIQ				
Mild cognitive deficit	7 (35)	3 (15)	1 (5)	0.000
Moderate cognitive deficit	1 (5)	0 (0)	0 (0)	
Borderline IQ	8 (40)	2 (10)	0 (0)	
Normal IQ	4 (20)	15 (75)	19 (95)	
PIQ				
Mild cognitive deficit	10 (50)	2 (10)	1 (5)	0.000
Moderate cognitive deficit	3 (15)	1 (5)	0 (0)	
Borderline IQ	6 (30)	7 (35)	0 (0)	
Normal IQ	1 (5)	10 (50)	19 (95)	
VIQ				
Mild cognitive deficit	4 (20)	0 (0)	0 (0)	0.003
Borderline IQ	5 (25)	2 (10)	0 (0)	
Normal IQ	11 (55)	18 (90)	20 (100)	

FSIQ, full-scale intelligent quotient; HD, hemodialysis; PIQ, performance intelligent quotient; RTx, renal transplantation; VIQ, verbal intelligent quotient.
Significance at $P<0.05$.

Table 3 Correlation between duration of hemodialysis and the Wechsler Intelligence Scale for Children in the hemodialysis group

WAIS	HD group (mean ± SD)	Duration of HD (month) (mean ± SD)	*P*-value	*r*
Information	6.90 ± 2.77	61.10 ± 34.10	0.751	−0.076
Comprehension	6.70 ± 3.06		0.833	−0.050
Arithmetic	4.65 ± 2.30		0.946	0.016
Similarities	9.15 ± 4.25		0.385	−0.205
Vocabulary	5.55 ± 3.28		0.780	−0.067
Digit span	6.25 ± 2.47		0.800	0.060
Picture completion	5.20 ± 2.44		0.438	−0.184
Picture arrangement	2.80 ± 2.33		0.057	−0.432
Block design	7 ± 1.59		0.352	−0.220
Object assembly	2.55 ± 2.01		0.239	−0.276
Coding	2.35 ± 1.87		0.378	−0.208
Mazes	3.65 ± 1.60		0.243	−0.274
PIQ	63.50 ± 12.79		0.195	−0.302
VIQ	86.05 ± 16.20		0.686	−0.096
FSIQ	73 ± 14.99		0.422	−0.190

HD, hemodialysis; FSIQ, full intelligent quotient; PIQ, performance intelligent quotient; *r*, correlation coefficient; VIQ, verbal intelligent quotient; WAIS, Wechsler Intelligence Scale.
Significance at $P<0.05$.

Table 4 Correlation between post-renal transplantation duration and the Wechsler Intelligence Scale for Children in the post-renal transplantation group

WAIS	Post-RTx group (mean ± SD)	Post-RTx duration (months)	*P*-value	*r*
Information	11 ± 4.21	28.10 ± 10.47	0.144	0.339
Comprehension	8.40 ± 3.62		0.001	0.674
Arithmetic	7.15 ± 3.39		0.884	0.035
Similarities	11.40 ± 2.93		0.030	0.485
Vocabulary	7.40 ± 3.32		0.001	0.700
Digit span	8.45 ± 3.56		0.966	0.010
Picture completion	8.60 ± 2.48		0.035	0.475
Picture arrangement	3.90 ± 2.25		0.034	0.475
Block design	7.75 ± 3.40		0.338	0.226
Object assembly	5.75 ± 3.48		0.195	0.302
Coding	5.85 ± 3.28		0.992	0.002
Mazes	5.95 ± 2.16		0.411	0.195
PIQ	82 ± 18.44		0.153	0.331
VIQ	104.15 ± 15.02		0.005	0.599
FSIQ	92.75 ± 17.49		0.020	0.517

FSIQ, full intelligent quotient; PIQ, performance intelligent quotient; R, Correlation Coefficient; RTX, renal transplantation; VIQ, verbal intelligent quotient; WAIS, Wechsler Intelligence Scale.
Significance at $P<0.05$.

because caregiver (parents) education may have a positive effect on the child's adaptation to school life, improving their attitudes and providing appropriate information and resources to aid their children's adjustment to school life.

The Wechsler Intelligence Scale showed significantly low scores for all subtests in patients more than healthy children as 40% of the HD patients and 15% of the post-RTx patients had mild to moderate cognitive deficits compared with the healthy controls.

Our results were in agreement with a study that assessed neurocognitive outcomes for 12 patients diagnosed with ESRD. Nine patients (mean age: 11 years) were compared with their healthy siblings (mean age: 10 years) on measures of intellectual and executive functioning, memory, and academic achievement. Patients' FSIQ scores were significantly lower than those of the sibling controls. For patients, FSIQ correlated negatively with total months on dialysis, as did WISC-IV Processing Speed. Patients' scores on the Metacognition Index of the Behaviour Rating Inventory of Executive Functions were significantly higher (indicating greater risk for dysfunction) than those of the siblings. Patients' scores on the Wechsler Individual Achievement Test-II-Abbreviated, total achievement, were significantly lower than those of their siblings. Younger age at transplantation was associated with higher scores on measures of processing speed as well as higher scores on measures of executive functioning, memory, and academic achievement [19].

Although some authors found no evidence of deleterious effects of ESRD on cognition [20–22], most studies have shown cognitive deterioration in children on dialysis [23,24].

According to the results, the means of PIQ and VIQ were lower than those of the control group; also, PIQ was significantly lower than VIQ in the HD group compared with the RTx group (Table 1).

Our results are in agreement with those of Falger *et al.* [25]. In their study, intellectual performance and motor performance were systematically assessed in 27 patients at a median age of 14.1 years and 6 years after RTx. Intellectual performance was analyzed using the WISC-III in 25 patients and by the Kaufman assessment battery for Children in two patients. Motor performance was evaluated by the Zurich neuromotor assessment. The median FSIQ was 97. Twenty-one patients had an FSIQ greater than or equal to 85. VIQ was significantly higher than PIQ [25].

It was clear from the results of the current study that the mean scores on VIQ, PIQ, FSIQ, and all subtests were significantly lower in the HD children compared with the post-RTx group and healthy children.

This confirms the results of previous studies that have documented lower IQ scores among children with ESRD compared with healthy children [9,19].

There was a positive statistically significant correlation between post-RTx duration and the following subtests of the WISC (comprehension, similarities, vocabulary, picture completion, picture arrangement) and also with VIQ and FSIQ.

These results were in agreement with a study carried out by Moser *et al.* [23], who studied the impact of chronic illness on neurocognitive development through a systematic review of publications that reported the developmental trajectory of patients with four childhood diseases: cystic fibrosis, hemophilia A, ESRD, and end-stage liver disease. Children with ESRD and end-stage liver disease show a mild cognitive deficit compared with the population norm [23].

In a study by Icard *et al.* [9], it was found that children with CKD who had undergone transplantation showed a significant increase in their intellectual/developmental functioning post-transplant compared with children with CKD who had not undergone transplantation. Although their overall intellectual/developmental level was not fully normalized, compared with the healthy control group, the change scores for the transplant group reflected over a 12-point increase, moving the group from the borderline range to the low average range of functioning. In this respect, pediatric transplantation appears to have a positive impact on the intellectual and developmental functioning of children with CKD [9].

Limitations

There are some limitations in this study; the percentage of participants with ESRD was relatively low. Another limitation is the scarce literature available for review of the impact of ESRD on the cognitive functions of children, especially literature from Arab countries.

Conclusion

In conclusion, advances in medicalzy care have clearly improved the outcome for children with ESRD. Better understanding of the neurocognitive function in children with ESRD is a critical element in providing early assessment programs and designing appropriate developmental interventions and educational support for this handicapping illness. In this context, with the aim of improving healthcare, there is an urgent need to carry out further studies to identify new risk factors that can impair the cognitive function, behavior, and quality of life of these patients. The identification of cognitive deficits may produce positive impacts on patient outcomes, particularly when the impairment is secondary to potentially treatable conditions such as depression and delirium.

Acknowledgements

The authors sincerely thank the patients and their families for participation, and also Dr Zeinab Sarhan, MD, Department of Psychiatry, Cairo University, Dr Dalia Ahmed, MD, Department of Public Health and Community Medicine, and Clinical Psychologist at Cairo University.

Conflicts of interest

There are no conflicts of interest.

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